DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

466 Fernandez Juncos Avenue
Puerta De Tierra
San Juan, Puerto Rico 00901-3223

May 22, 2001

WARNING LETTER
SJN-01-13

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Carlos Santiago
General Manager
Zenith Laboratories Caribe, Inc.
PO Box 11979
Cidra, PR 00739-1979

Dear Mr. Santiago:

From February 1, 2001 to April 3, 2001, two investigators from The San Juan District Office of the Food and Drug Administration conducted an inspection of your prescription drug manufacturing facility, Zenith Laboratories Caribe, Inc., located at Rd. 734 Km 0.3 Cidra Industrial Park, Cidra, PR 00739. Our evaluation of the information obtained during the inspection determined that the pharmaceutical products manufactured by the facility are adulterated within the meaning of section 501(a)(2)(b) of the Federal Food, Drug and Cosmetic Act because they were not manufactured in accordance with Good Manufacturing Practice Regulations (GMP) as defined in Tittle 21, Code of Federal Regulations, Part 211 (21 CFR 211).

The deficiencies found during the inspection, and reported on the List of Inspectional Observations, FDA-483, presented at the conclusion of the inspection include the following:

Quality System

1. Failure to a have an adequate tracking system to evaluate the trend of your failure investigations to assure that systemic problems are corrected. This deficiency affects your stability program, laboratory OOS, and manufacturing processes. [21 CFR 211.22] For example:

Stability Program

(a) Failure to place in your stability program 13 validation batches and 2 annual batches manufactured from 1999 to 2001. Some of the products affected are Tolazamide tablets, Pindol tablets, Clozapine tablets, Doxycycline Hyclate capsules, Probenecid tablets, Phenytoin Sodium capsules, Doxazosin Mesylate tablets, Labetalol HCl tablets, and Tetracycline HCl capsules. [21 CFR 211.166 (b)]

Laboratory /Analyst Errors (OOS)

(b) Failure to train all your laboratory personnel when the cause of the OOS result indicates that it was an analyst error to avoid recurrence of the same practice. [21 CFR 211.25]

Manufacturing operations

(c) Failure to have adequate procedures in the packaging operations to prevent discrepancies and failures.[21 CFR 211.100]

2. Failure to validate, as part of your method transfer studies, all analytical methods used during cleaning validation studies, to demonstrate that they have the accuracy, sensitivity, specificity, and reproducibility as required by CFR 211.165 (e) and to assure that equipment used for the manufacturing of human drugs is being thoroughly cleaned as required by 21 CFR 211.67 (a).

3. Failure to assure that stability lot [redacted] of Diazepam 2mg tablets was within specifications for impurity MACB, between the 18 to 24 month stability interval. This impurity was at its upper limit at the 18-month stability interval and it was out of specifications when it reached the 24 month interval. You also failed to investigate if other lots of Diazepam manufactured around the same time were also affected. [21 CFR 211.160 (b) and 21 CFR 211.192]

4. Failure to file an ANDA Field Alert (ANDA 71-307) for lot [redacted] of Diazepam 2 mg tablets that failed stability at the 24 month interval. The results for impurity MACB (2-Methylamino-5-chlorobenzophenone) was 0.02%. The ANDA specification for this impurity is NMT 0.01%. [21 CFR 314.98 (c)]

We acknowledge receipt of your response letter dated May 4, 2001, and signed by Ms. Lelia M. Fuentes and by you. We evaluated your response and it is our conclusion that some of the issues found during this inspection are systemic deficiencies that need your prompt attention. As stated in your response, please provide us quarterly reports on the status of your commitments to address the FDA 483 observations.

Neither this letter nor the list of inspectional observations is meant to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these violations, and you should establish procedures whereby such violations do not recur. Failure to promptly correct these deviations may result in regulatory action without further notice. These sanctions include, but are not limited to, seizure and/or injuction.

Please notify the San Juan District office in writing, within 15 working days of receipt of this letter, of your corrections to the violations identified in this letter.

Corrective actions addressed in your previous letter may be referenced in your response to this letter as appropriate.

Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernandez Juncos Avenue, San Juan, Puerto Rico 00901-3223, Attention: Margarita Santiago, Acting Compliance Officer.

Sincerely,

Mildred R. Barber

Mildred Barber
District Director